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Kidney Tumors in Children

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Abstract

Wilms tumor (WT) is an embryonal tumor of the kidneys. It is associated with many oncogenic genetic aberrations and congenital anomalies. Owing to worldwide clinical research and optimized patient care, curative therapy can be obtained in 90% of diagnosed children with WT. The decision of treatment mainly depends on stage, age, histological type, and genetic markers. Except for WT; congenital mesoblastic nephroma, clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma constitute 5% of kidney tumors. Herein, WT and other tumors of the kidney will be emphasized.

Keywords: Wilms tumor, unfavorable histology, kidney tumors

Introduction

Childhood malignant kidney tumors are responsible for approximately 5,5-7% of childhood cancers.[1,2] About 95% of these kidney cancers are Wilms tumor (WT). As a survival advantage is provided with all childhood cancers, the 5-year overall survival for WT is around 93%.[2] Less common types of renal tumors consist of clear cell sarcoma, malignant rhabdoid tumor, congenital mesoblastic nephroma, and cystic differentiated nephroblastoma.[1-3]

1. Wilms Tumor

As mentioned earlier, WT is the most commonly seen renal neoplasia of childhood. Under the age of 15, the incidence is 10.4 cases in one million children and also 0.2 cases per 10,000 infants.[1-4] More than ninety-five percent of patients are diagnosed under 10 years of age. The mean age at diagnosis is about 44-47 months.[5] Around 10% of diagnosed patients present a congenital malformation syndrome, which can enable early diagnosis.[5,6]

1.a. Genetic landscape

Sixty percent of the patients who have congenital anomalies and WT, present nephrogenic rests. Congenital anomalies are composed of hemihypertrophy and also urinary tract anomalies, such as cryptorchidism and hypospadias.[7] The phenotypic syndromes and congenital malformations associated with WT can be found in **Table 1**.

One of the most important genetic alterations which have a remarkable impact on pathogenesis is the loss of the *WT1* gene. WT1 which is a tumor suppressor gene, plays a significant role in cell development, differentiation, and apoptosis. The disease is usually associated with biallelic inactivations of the gene. Wilms tumor, aniridia,

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genitourinary anomalies, and mental retardation (WAGR) syndrome is a WT1-related spectrum, which occurs with the interstitial deletion on chromosome 11 (del(11p13)).[8] The clinical features are aniridia, genitourainary anomalies, and mental retardation. In children with WT, the incidence of this deletion is around 0.4%. The risk of WT development in WAGR syndrome is about 50%, with presenting earlier with a median age of 22 months. In addition to this, WT in children with WAGR tends to be bilateral involvement.[9,10] The other syndromes related to the WT1 gene are Denys Drash and Frasier syndromes. As a part of Denys Drash syndrome, missense germline mutations of WT1 are associated with WT and the risk of WT development is as high as 90% in children with Denys Drash syndrome. However, in Frasier syndrome splice-site mutations are present in WT1 and this syndrome has a lower incidence for WT development.[8-11]

Mutations in the *WT2* gene are also important genetic alterations playing a role in WT development. Altered genetic expressions of two gene clusters located in the WT2 locus which is chromosome 11p15.5 are responsible for Beckwith-Wiedemann syndrome (BWS). Generally, the syndrome is presented with an asymmetric overgrowth of one or more parts of the body. Kidney abnormalities and also hypoglycemia, especially in neonates, can be observed. BWS predisposes to rhabdomyosarcoma, WT, and hepatoblastoma development, especially in the first decade of life.[12,13] Previously, the incidence of BWS in children who have WT was about 1%. However, with the latest population-based studies, the incidence of BWS in patients who have been diagnosed with WT is reported as high as 16%.[14] Besides, the risk of developing WT is higher in the presence of hemihyperthrophy.[15]

Despite all the genetic alterations, which are already known to have a role in pathogenesis and are still being studied, there is also an entity called Familial WT. About 2% of patients with WT have a positive family history of WT. However, the risk for WT development in siblings and offsprings of patients who are diagnosed with sporadic WT is about 1% and 2%, respectively.[16] Two loci have been identified as associated with familial WT, which are 17q12-q21 (FWT1) and 19q13.4 (FWT2).

The genomics of WT have been highly studied as in many other solid tumors of childhood. However, there is a noteworthy study about the genomic landscape of WT, conducted by Gadd et al.[17] This study provided genome-wide sequencing, mRNA, and miRNA expression, also DNA copy number, and methylation analysis on a very large scale. This study has made significant contributions to our understanding of the genetic background of WT, as follows. Firstly, more than one genetic event has an impact on WT development. Different genetic aberrations result in different methylation and gene expression patterns of WT. Also, a large number of candidate genes play a role in WT development, however, most of them are mutated only in less than 5% of WTs. Once and for all, WT arises from recurrent mutations affecting early renal development or either epigenetic regulation.[17]

Children followed up with BWS or other overgrowth syndromes, WAGR, and Denys-Drash, also sporadic aniridia, or isolated hemihypertrophy have significantly increased risk for WT development. Therefore, screening is recommended in such cases, with the primary goal of earlier detection of a small and localized tumor (stage I or II), improve prognosis, and use of less intensive treatment.[18]

1.b. Clinical features

An asymptomatic abdominal mass is the most common presenting symptom, detected generally by the parents when they are bathed or dressed or by pediatricians on a well-child visit. A large, non-tender flank mass is

Table 1.
Syndromes and congenital malformations associated with Wilms Tumor

Overgrowth pheynotype	Non-overgrowth pheynotype
High risk for WT (>20%)	**High risk for WT (>20%)**
Perlman syndrome	WAGR syndrome (WAGR spectrum)
	Denys-Drash syndrome
	Fanconi anemia with biallelic mutations in BRCA2 (FANCD1) or PALB2 (FANCN)
Moderate risk for WT (5-20%)	**Moderate risk for WT (5-20%)**
Beckwith-Wiedemann syndrome	Frasier syndrome
Simpson-Golabi-Behmel syndrome	
Low risk for Wilms Tumor (<5%)	**Low risk for Wilms Tumor (<5%)**
DICER1 syndrome: DICER1 mutation	Bloom syndrome
Isolated hemihypertrophy	Li-Fraumeni syndrome
PIK3CA-related segmental overgrowth including CLOVES syndrome	Hyperparathyroidism-jaw tumor syndrome
9q22.3 microdeletion syndrome	MULIBREY nanism syndrome
Sotos syndrome	Familial Wilms tumor
	Genitourinary anomalies
	Sporadic aniridia
	Trisomy 18

CLOVES; Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal/spinal abnormalities, MULIBREY; Distinctive abnormalities of the (MU)scles, (LI)ver, (BR)ain, and (EY)es, WAGR; Wilms tumor, aniridia, genitourinary anomaly, and mental retardation

usually present. Abdominal pain can accompany in about 40% of patients. A distinguishing finding from the splenomegaly of this mass is that this mass does not move with respiration in the physical examination.[19] Gross and microscopic hematuria occurs in 18% and 24% of patients on admission, respectively. As well, hypertension is another presenting symptom, seen in about 25% of patients, which is caused by activating the renin-angiotensin system. The other less common symptoms on admission can be listed as follows; hypercalcemia, fever, anorexia, and weight loss.[19-21]

Apart from the most common findings, pulmonary symptoms such as dyspnea can be observed in patients owing to pulmonary metastasis. In the case of pulmonary embolism, emergency medical intervention is crucial. Also, the tumor can develop subcapsular hemorrhage, leading to rapid abdominal enlargement, anemia, and severe pain.[19-21] Acute abdomen due to tumor rupture, paraneoplastic polycythemia, Budd-Chiari syndrome, heart failure due to tumor thrombus, and acquired von Willebrand deficiency have been reported.[22] As mentioned earlier congenital abnormalities can be observed in 12-15% of patients in physical examination and imaging studies[23].

1.c. Diagnostic evaluation, differential diagnosis, histology, and staging

As with every diagnostic evaluation in pediatrics, a complete history and physical examination are the first steps. Patients should be judged carefully for signs of associated syndromes such as aniridia, developmental delay, genitourinary anomalies, and hemihypertrophy. The first tests to be performed are whole blood count, urinalysis, biochemical tests, coagulation parameters, and cardiac evaluation.

Generally, the first chosen imaging method is abdominal ultrasonography. However, computed tomography (CT) and/or magnetic resonance imaging (MRI) with contrast are more definitive imaging methods. MRI of the abdomen needs moderate to deep sedation, which is a common concern for clinicians. On the other hand, MRI supplies excellent detail, especially in the case of bilateral involvement and liver metastasis. Detection of contralateral lesions is essential since the stage and treatment of the patient are based on the extent of the tumor.[24,25] The decision of surgical approach or preoperative chemotherapy should be made with the results of imaging studies. In a study carried out by The SIOP-Renal Tumor Study Group (RTSG), online questionnaires were applied to the experts who currently work in the field of pediatric tumors. The aim was to determine pathognomonic imaging findings of pediatric kidney tumors. In this study, WT was generally described as a solid intrarenal mass, with a pseudo capsule, and appears to be heterogenous owing to the hemorrhage, necrosis, and/or cysts inside the tumor. However, it is emphasized that the diagnostic process is not solely based on the MRI findings. In addition to MRI findings, age on admission, and clinical presentation contributes to the differential diagnosis.[26]

Compared with an MRI, a CT scan of the abdomen also confirms a mass of renal origin easily and also provides information about bilateral involvement.[24] However, small bilateral tumors can be missed in helical CT scans. Another important issue about preoperative diagnostic imaging is to determine the intravascular extension of the tumor. Inferior vena cava, atrial involvement, and renal vein involvement should be demonstrated preoperatively to guide safe management. CT scans have been reported to establish cavoatrial thrombus precisely.[27] Radiation exposure is a concern about CT. Nonetheless, a CT scan is a rapid procedure, supplies continuous imaging of the abdomen and chest, with perfect chest detail. The most common metastasis sites in WT are the lungs and liver with 85% and 10%, respectively in metastasized patients. Therefore, imaging of the lungs is vital. CT scan is the most sensitive modality for detecting lung metastasis and pleural effusions.[28,29]

Evaluating the other imaging methods; Fluorine F 18-fludeoxyglucose positron emission tomography (FDG-PET)-CT is not routinely used. Also, there is no need to use a chest X-ray. In the presence of extrapulmonary metastasis, a bone scan or a cross-sectional assessment of the affected site should be considered.[28]

It should be underlined that a definitive diagnosis is only possible with pathological evaluation. However, in a resectable renal mass, such as stage I or II WT, the biopsy is not recommended since it will upstage the tumor to stage III, owing to tumor cells spread during the biopsy. However, in some cases, primary nephrectomy is not possible. In preoperative studies, lymph node status, intravascular extension, and tumor rupture should be judged and clarified. Therefore, a biopsy should be undertaken. In the presence of extended tumor thrombus to the hepatic veins level, tumor involving contiguous organs in which a complete resection can not be possible without the resection of these organs, and extended pulmonary and liver metastasis, primary nephrectomy is not the first choice. After the biopsy, the patient should be treated as stage III. With obtaining a biopsy, histological evaluation can be possible. However, deciding on the tumor histology can be controversial, owing to the heterogeneity of WT.[30]

Neuroblastoma, other kidney tumors, hematoma, and multicystic dysplastic kidney should be taken into account in the differential diagnosis. In the case of blastemal cell predominance, all small round blue cell tumors should be included in the differential diagnosis.[31]

WT exhibits a triphasic histological structure composed of blastemal, epithelial, and stromal cells. However, not all tumors appear to be triphasic. Anaplastic histology is solely the most significant prognostic factor predicting treatment response and survival. Anaplasia occurs in older patients. Two criteria must be met to say anaplasia, which is the presence of hyperchromasia and multipolar polyploid mitotic figures with a marked nuclear enlargement.[32]

The staging system has been developed by National WT Study (NWTS) Group and depends on the pathological, histological, and surgical findings.

Detailed explanations of the staging system are available in **Table 2**. Lymph node sampling and evaluation are recommended in all stages. Generally, 43% of patients are diagnosed with a stage I tumor. However, it should be underlined that regional lymph node evaluation is strongly recommended in these low-risk patients too. As well, lymph nodes should be negative for stage II patients. Tumor rupture, spill to the flank during the surgery, and any kind of biopsy performed before surgery are defined as stage III tumors. Besides the stage, histology has an impact on the outcome and is indicated with the stage.[20] In stage V patients, treatment after definitive surgery relies on the highest stage of the remaining kidneys and the posttreatment pathology.[33]

1.d. Treatment and prognosis

Currently, two treatment approaches are being implemented in the treatment of WT, which are conducted by two large study groups working on WT, the Children Oncology Group (COG), and the International Society of Paediatric Oncology (SIOP). In the COG approach, upfront surgery is recommended, whereas the SIOP approach depends on preoperative chemotherapy in the first step. Postoperative chemotherapy and radiation in selected patients are mutual treatment methods for the two groups. As well, patients younger than 6 months are treated with primary surgery in both groups.[34,35]

Conditions, in which primary nephrectomy is not recommended, are mentioned earlier. In the management of unilateral WT, the COG approach recommends nephrectomy and adjuvant chemotherapy. Whereas, SIOP suggests a neoadjuvant chemotherapy period prior to the surgery. The chemotherapy regimen depends on the stage and the histological findings of the tumor. On the other hand, in the presence of a tumor weight less than 550 gr, age <2 years, and stage I tumor with favorable histology; the necessity of chemotherapy is controversial. These patients can be cured with surgery alone.[36] Radiotherapy (RT) is advised in stage III and IV patients, and it should be underlined that owing to the long-term side effects, the requirement of RT should be evaluated carefully. RT is strongly recommended for patients with unfavorable histology.[37] Recently, the Renal Tumor Study Group (SIOP-RTSG Umbrella), which is a current update of SIOP protocol, recommends the decision of adjuvant RT in localized tumors should be undertaken based on tumor stage and pathologic findings after neoadjuvant chemotherapy and surgical features such as the presence of residual disease, evaluation of resection margins, tumor spillage, also lymph node involvement, and presence of drug-resistant viable tumor cells, as well as histological risk stratification.[38,39] As well, the timing of RT is a highly studied topic in WT treatment. A recent study from National Cancer Database revealed that, in non-metastatic WT adjuvant RT administered within 14 days (≤14 days) after surgery, is related to improved survival.[40]

Once and for all, comparing the two treatment approaches, in the COG approach, initial nephrectomy provides early and accurate histological diagnosis unamended by chemotherapy and staging information. On the other hand, in the SIOP approach, definitive surgery after a preoperative chemotherapy period achieves less tumor spills throughout surgery and also lower stage. Compared with the histological analyzes of primary nephrectomy, histological findings after a preoperative chemotherapy period result in less blastemal and mixed histology types.

WT with favorable histology has a survival rate greater than 90%. In general, improvements in patient care and management of side effects in childhood cancers have resulted in significant survival advantages. Besides

Table 2.
Staging system for Wilms Tumor

Stage	Definiton
Stage I	-Tumor is limited to kidney and completely resected. -Renal capsule is intact. -No tumor ruptures and biopsies before surgery. -Renal sinus vessels are not involved. -Margins of resection or beyond margins are tumor free. -All sampled lymph nodes are tumor negative.
Stage II	-Tumor is entirely resected and there is no sign of residue. -Regional extension of the tumor (permeation of the renal capsule, or widespread invasion of the soft tissue of the renal sinüs). -Blood vessels outside the renal parenchyma, in the nephrectomy specimen, including those of the renal sinus contains tumor cells. Margins are clear.
Stage III	-There is a postsurgical residue. -Abdominal or pelvic lymph nodes are involved with tumor. -Surface of peritoneum is involved with tumor and contains tumor implants. -Gross or microscopic tumor maintains postoperatively. -Tumor is not entirely resectable because of the involvement of vital organs. -Tumor has ruptured before surgery or spillled during surgery. -Any type of biopsy is undertaken, before surgery. -Tumor is extracted more than one piece owing to the contagious organ involvement. -Even outside the abdomen, extension of tumor to the vena cava thoracicus and heart is taken into account as stage III.
Stage IV	-Hematogenous metastases (lung, liver, bone, brain) -Metastatic lymph nodes outside the abdominopelvic region. -Involvement of adrenal gland by the tumor is not regarded as metastasis and staging depends on all other existing parameters.
Stage V	-Bilateral involvement of kidneys on admission.

these, shortened length of therapy, dosing of irradiation, fields irradiated, and also tailored irradiation therapy have significant contributions to survival and prognosis. Histopathological characteristics and stage have an important effect on prognosis, as mentioned earlier. Besides, another well-known prognostic marker is age on admission. Older age at diagnosis is associated with poor prognosis.[41] On the other hand, in the era of genetic research, molecular markers are documented to have an impact on prognosis. Among them, the most potent predictor of outcome which is associated with adverse outcomes is 1q gain. 1q gain is present in approximately 28% of the cases. Also in low-risk patients; loss of heterozygosity of 11p15 is involved with adverse prognosis and generally relapses.[42]

2. Non-Wilms Tumors

Non-WTs constitute a rare part of childhood kidney tumors. However, controversial to their rarity, sufficient diagnostic management and rapid diagnosis are crucial, owing to the high morbidity and mortality.[43]

2.a. Clear cell sarcoma of the kidney

Clear cell sarcoma of the kidney is an infrequent kidney tumor, presenting between 2-3 years of age. Bone metastasis is present in most cases, therefore bone scintigraphy should be undertaken in staging studies. However, in relapses, brain involvement is present more than bone. Recently, internal tandem duplications in BCL-6 coreceptor (BCOR) and a translocation t(10;17) creating the fusion gene *YWHAE-NUTM2B/E* have been reported to be associated with tumors. The course of the tumor is much more aggressive and recurrent compared to WT. Owing to the intensive treatment regimens, the overall survival has been improved to 86%.[44]

2.b. Congenital mesoblastic nephroma

Congenital mesoblastic nephroma commonly develops in the early infancy period with a median age of 3 months. It may present with abdominal distension, hypertension, hematuria, anemia, vomiting, and hypercalcemia. Curative treatment in most cases is surgery. Patients >3 years of age, cellular type histology, and stage III tumors should be pursued very closely as the disease may recur.[45]

2.c. Renal cell carcinoma

Renal cell carcinoma is the most prevalent kidney tumor in adults, whereas it is rare in childhood. In the presence of localized disease, surgery is the sole treatment method, however in metastatic disease the role of postoperative chemotherapy is controversial and the response is poor. Even though, there is limited evidence, sunitinib, mTOR inhibitors, and also anti-VEGF inhibitors are recommended in metastatic patients.[46]

2.d. Renal medullary carcinoma

Renal medullary carcinoma is a very seldom and very fatal tumor of the kidneys. This tumor almost always develops in patients with sickle cell disease (SCD) or carriers of SCD. There is no standardized treatment method and also owing to the sparseness of the tumor, the screening of patients with SCD is not recommended.[47]

2.e. Malignant rhabdoid tumor of the kidney

In childhood, malign rhabdoid tumor of the kidneys accounts for 1.5-4% of renal malignancies, being a part of the malign rhabdoid tumor family, which are very invasive tumors mainly developing in pediatric age. Other sites, such as the central nervous system, lungs, bone, and soft tissues should be evaluated. Lungs are the most frequent site for metastasis. Patients under the age of 24 months and the existence of distant metastasis are poor prognostic criteria.[48]

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